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PORTNER, VIRGINIA ALLEN

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Please find below and/or attached an Office communication concerning this application or proceeding.

File Copy

Office Action Summary	Application No. 09/284,233	Applicant(s) Meyer
	Examiner Portner	Art Unit 1645

-- The MAILING DATE of this communication appears on th c ver sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Dec 14, 2001* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-11 and 13-22* is/are pending in the application.

4a) Of the above, claim(s) *16* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-11, 13-15, and 17-22* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims *1-11 and 13-22* are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Claims 1-11, 13-22 are pending.

New claim 22 has been submitted.

Claim 16 remains withdrawn from consideration

Claims 1-11, 13-15 and 17-22 are under consideration.

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 14, has been entered.

Response to Amendment/Declaration submitted by Dr. Meyer

2. The declaration submitted by Dr. Thomas F. Meyer under 37 CFR 1.132 filed August 22, 2001 is insufficient to overcome the rejection of claims 1-11, 13-15, 17, 19-21, and newly submitted claim 22, based upon Michetti in view of Russell or Russell in view of Bukanov as set forth in the last Office action because:

The Declaration utilized a strain of Salmonella designated SL3261::YZ222. This strain does not evidence original descriptive support in the instant specification.

Strain SL3261::YZ222 is described to be a ▲ thyA strain that contains a stabilized plasmid encoding thyA gene as a means for a balanced lethality to complement the chromosomally deleted thyA. This type of mutant strain is not described in the instant specification.

Three different promoters for expression were utilized, P_{phoP}, P_{nirB} and P_{T7}. Only P_{T7} evidences original descriptive support in the instant specification, description of P_{phoP}, P_{nirB} could not be found in the instant specification.

Four different H.pylori antigens encoded by plasmids in strains CREA 1396, 1398, 1402,1404,1412, 1467, 1468. The strains used to immunize a host were not described in the instant specification.

Of the combinations of expression signals, various antigens and constructs, shown in Exhibit 1, none of the combinations, were described in the instant specification. Of the four antigens encoded on the plasmids, only H.pylori urease and heat shock protein were found in the instant specification. Original descriptive support for HylB and citrate synthase homolog was not found for these two antigens.

The strains that evidenced the fewest colony forming units after challenge were CREA 1467 and 1468, which utilized P_{phoP}, or P_{nirB} promoters, both of which do not evidence original descriptive support in the instant specification. The nirB promoter is known to be induced up to 20 fold under anaerobic conditions (see Goldman et al, 1991, reference previously provided).

The Declaration does not present data commensurate in scope with the claimed invention.

Objection/Rejections Withdrawn

Specification

3. The heading prior to the brief description of the figures on page 10, line 12 has been entered.

Rejections Maintained

4. Claims 1-11, 13-15 and 17-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the production of recombinant DNA, vectors, host cells, chimeric proteins and antigenic compositions that comprise Helicobacter antigens the instant specification, does not reasonably provide enablement for preventive or therapeutic live vaccines that express any Helicobacter antigen, and compositions which comprise any nucleic acid sequence from Helicobacter as the active agent which is a ~~mimeotope~~ mimotope or immunogen that is encoded by a nucleic acid sequence that does not evidence original descriptive support. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, for reasons of record in paper number 10, paragraphs 13 and 14.

Please Note: The following prior art rejections are being maintained in light of claims 2, or claims 8-11, 14-15, 17-21 broaden the scope of claim 1 to encompass any enterobacterial cell or

attenuated pathogen, respectively. The scope of claim 1 includes the enterobacterial cells of claim 2 or attenuated pathogens of claims 8-11, 14-15 and 17-21, and for at least this reason the following rejections are being maintained.

5. Claims 1,2,5 and 10 rejected under 35 U.S.C. 102(b) as being anticipated by Evans et al (1993) for reasons of record in paper number 10, paragraph 16.

6. Claims 1-2, 5-6,7-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Odenbreit et al (April 1996) for reasons of record in paper number 10, paragraph 17.

7. Claims 1-2, 5, 10, 11,13, 17-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Doidge (WO95/33482) in light of McKee (1992) for reasons of record in paper number 10, paragraph 18.

8. Claims 1,2,4,5, 10, 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Dore'-Davin et al (May 1996) for reasons of record in paper number 10, paragraph 19.

9. Claims 1-2,4-5,10-11, 13-15, 17-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Michetti (WO95/22987) for reasons of record in paper number 10, paragraph 20.

10. Claims 1-11,13-15, 17-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Michetti (WO95/22987) in view of Russell et al (US Pat. 6,030,624) for reasons of record in paper number 10, paragraph 22.

11. Claims 1-4,7-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Russell et al (US Pat. 6,030,624) in view of Bukanov et al (1994) for reasons of record in paper number 10, paragraph 23.

Response to Arguments

12. Applicant's arguments filed December 20, 2000 have been fully considered but they are not persuasive.

13. Applicant argues the rejection of claims 1-12, 13-15 and 17-21 under 35 U.S.C. 112, first paragraph (scope), by asserting the efficiency of Helicobacter (urease) proteins can be increased by expression from a heterologous live attenuated bacterium, and the live vaccine administered as an oral vaccine results in about 100% protection in a single dose.

14.In response, to the Arguments presented in pages 8-9 of Applicant's Amendment dated December 20, 2000, it is the position of the examiner that the arguments set forth are not commensurate in scope with the claimed invention. The independent claim is directed to the use of any attenuated microbial pathogen and is not limited to the presentation of urease immunogenic polypeptides or ~~mimeotopes~~ mimotopes in an attenuated Salmonella pathogen. Claim 1 may use any

attenuated microbial pathogen, which would include viruses, and other attenuated bacterial pathogens and is not limited to urease, a known protective Helicobacter immunogen.

Immunogens are not by nature automatically protective as asserted by Applicant. Immunogens will induce an immune response, but the immune response need not be protective against infection and disease and useful in the treatment or prevention of Helicobacter infection. Immunogens can induce diagnostic immune responses that do not eradicate infection; this is true of the long standing chronic infection caused by Helicobacter.

The scope of enablement rejection is maintained for reasons of record in paper number 10, paragraphs 13 and 14.

15. Applicant argues the rejection of claims 1,2,5 and 10 under 35 U.S.C. 102(b) as being anticipated by Evans et al (1993) by asserting that:

> Evans et al "makes no mention of any medical applications of this protein, nor demonstrates that immunization with the adhesin subunit leads to the development of a protective immune response." and concludes
>
> "Evans et al. clearly does not disclose the immunogenic recombinant attenuated microbial pathogen of the present invention."

16. In response to Applicant's assertion with respect to the application of Evans et al as anticipating the claimed compositions, it is the position of the examiner that Applicant's arguments are not commensurate in scope with the claimed invention of claims 1,2,5 and 10. Claim 2 is not limited just

to Salmonella, but may be any type of entero-bacterial cell. Evans et al used E.coli, which is an entero-bacterial cell for the production of an attenuated microbial pathogen that expresses a heterologous Helicobacter immunogen.

The expressed Helicobacter antigen was immunostimulatory, immunoreactive and used to detect the adhesin binding sequences for host epithelial cells. An immune response, obtained from immunization with the adhesin receptor sequence synthesized peptide, blocked hemagglutination of human erythrocytes by H.pylori (page 682, col. 2, paragraph 2), a type of protective immune response.

No evidence has been made of record to show that the immunogen of Evans is not able to induce a protective immunity. Inherently the compositions that comprises an attenuated microbial pathogen anticipates the now claimed invention. Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594

17. The rejection of claims 1-2, 5-6,7-10 under 35 U.S.C. 102(b) as being anticipated by Odenbreit et al (April 1996) is argued:

"Odenbreit et al. makes no mention of medical applications of these truncated Helicobacter antigens, nor were any immunological studies performed" and asserts that "no indication that these antigens are capable of inducing a protective immune response." and further asserts that "[T]hese cells do not express a heterologous Helicobacter adhesin protein. Instead, these cells lack expression of the natural Helicobacter adhesin subunit, due to the transposon insertion within the gene.

18. Applicant's arguments filed with respect to Odenbreit have been fully considered but they are not persuasive because the claimed invention is not limited to an expressed protein, but may be any expressed Helicobacter polypeptide to include ~~mimeotopes~~ mimotopes that are immunogenic.

Contrary to Applicant's assertion that the polypeptides were not expressed, the transformed strain P1-140 expressed the adhesin polyeptide but at a very reduced level, approximately 10% of that of wild-type strains. (see page 366, col. 2, paragraph 2 and page 367 both columns at bottom of page). The open reading frames were determined to *correspond to* nucleic acid sequences that encode adherence proteins as shown through the disruption of bacterial binding to the corresponding receptors on eukaryotic cells. (See page 369, col. 2). The disclosed mutant strain of E.coli that encoded the heterologous nucleic acid sequence (plasmid used to produce clone P1-140) would be capable of causing the expression of the nucleic acid molecule in a target cell and anticipates the now claimed invention.

With respect to the assertion that the reference did not conduct any immunological studies, Applicant is referred to page 371, col. 1, paragraph 2, which discloses an immunological method used in obtaining information for the published paper.

The claimed compositions, that comprise a recombinant attenuated microbial pathogen that expresses a heterologous Helicobacter antigen, are disclosed by Odenbreit et al. The recombinant attenuated microbial pathogens inherently anticipate the now claimed compositions.

No evidence has been made of record to show that the composition of Odenbreit is not capable of being immunogenic. If applicants contend that this is not the case, applicants are advised that the Office does not have the facilities for examining and comparing applicant's product with the prior art, and that the burden is on applicant to show a novel or unobvious difference between the claimed method and the method of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594

19. The rejection of claims 1-2, 5, 10, 11,13, 17-21 under 35 U.S.C. 102(b) as being anticipated by Doidge (WO95/33482) in light of McKee (1992) is argued by asserting:

"Doidge et al. merely lists McGhee et al. as well as numerous other articles in a section entitled "References" and therefore "McKee et al. is improperly cited as part of this rejection.";

McKee is argued to teach the importance of a balanced Th1 and Th2 immune response but does not provide how such an appropriate balance could be obtained for Helicobacter; and

"Doidge et al proposes that a recombinant Helicobacter live vaccine might be used for treatment of Helicobacter infections, no such evidence was presented."

20. Applicant's arguments filed with respect to Doidge have been fully considered but they are not persuasive because at page 8, line 19, the teachings of both Holmgren and McGhee are incorporated by reference, and not just listed in the References section as asserted by Applicant.

The claimed invention is not directed to a method of obtaining a balanced Th1 and Th2 immune responses, but is directed to recombinant attenuated bacterial pathogens that express heterologous Helicobacter antigens for the induction of an immune response and the use of the attenuated microbial pathogen in a method of inducing an immune response.

The Doidge reference discloses and claims recombinant host cells that express a heterologous Helicobacter antigen, and in light of McGhee, the person of skill in the art would have known how to make and use the live recombinant microbial pathogens of Doidge. The reference also teaches the use of live viral vectors, as well as other live vaccine vectors that would express Helicobacter catalase in a method of inducing a protective immune response; formulation of these compositions for oral and parenteral administration to a host is taught (see all claims).

No evidence has been made of record to show that the composition of Doidge is not capable of being immunogenic. If applicants contend that this is not the case, applicants are advised that the Office does not have the facilities for examining and comparing applicant's product with the prior art, and that the burden is on applicant to show a novel or unobvious

difference between the claimed method and the method of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594

21. The rejection of claims 1,2,4,5, 10, 17 under 35 U.S.C. 102(b) as being anticipated by Dore'-Davin et al (May 1996) is argued:

to "not disclose the use of any live vaccine";

"nor does Dore-Davin disclose any Helicobacter antigen capable of inducing protective immunity";

nor does the reference "contain any data indicating that the application of a live vaccine consisting of the recombinant bacteria expressing the Helicobacter antigen induces immunological protection in a host."

22. Applicant's arguments filed with respect to Dore'-Davin have been fully considered but they are not persuasive because the claimed invention is directed to recombinant attenuated microbial pathogens that express a Helicobacter heterologous immunogen, wherein the immunogen is capable of inducing a protective immune response. Applicant's arguments are directed to methods of treating and preventing infection, not the compositions of claims 1,2,4,5,10 and 17, and are therefore not commensurate in scope with the claimed inventions to which the Dore-Davin reference was applied. Dore-Davin clearly shows the production of a recombinant attenuated microbial pathogen that expresses an immunogen capable of inducing a protective immune response.

The immunogen of Dore-Davin is Helicobacter urease polypeptide, expressed by a recombinant attenuated microbial pathogen, and therefore meets the claimed invention. Any and all Helicobacter antigens need not be expressed simultaneously by the claimed recombinant attenuated microbial pathogen, only a single Helicobacter immunogen need be heterologous to the attenuated pathogen.

The rejection is maintained for reasons of record.

23. The rejection of claims 1-2,4-5,10-15 under 35 U.S.C. 102(b) as being anticipated by Michetti (WO95/22987) is asserted to:

disclose "only the use of purified, enzymatically inactive urease with cholera toxin as an adjuvant as a formulation for oral immunization"; and

Michetti et al is further asserted to not teach the use of an adjuvant that is "suitable for use in humans." and concludes

"Michetti et al. thus does not disclose the protective Helicobacter immunogen of the present invention.

24. Applicant's arguments filed with respect to Michetti have been fully considered but they are not persuasive because Applicant's arguments are not commensurate in scope with the claimed invention.

With respect to the type of heterologous Helicobacter immunogen contained in the attenuated microbial pathogen, it is the position of the examiner that the claimed invention is not limited to only those urease immunogens that are enzymatically active. Within the scope of the

claimed invention are ~~mimeotopes~~ mimotopes of urease. These immunogens are not enzymatically active, though immunogenic. Therefore, arguments directed to the lack of enzymatic activity ~~is~~ are not commensurate in scope with the claimed invention.

The claimed method is a method of treating a patient, the patient may be any type of patient and is not limited to humans, even if the methods were limited to humans, the reference teaches the use of mucosal adjutants and parenteral adjutants, multiple modes of formulation of the compositions and the use of cholera toxin B subunit that has reduced toxicity.

With respect to Applicant's argument that states, "Michetti et al. thus does not disclose the protective Helicobacter immunogen of the present invention", it appears that Applicant is arguing the specific strain of Salmonella transformed with the specific plasmid used in the immunization of the instant Specification. This specific species of attenuated microbial pathogen is not recited in the claims. Applicant's argument is not commensurate in scope with the claimed invention.

25. The rejection of claims 1-11,13-15 and 17, 19-20 under 35 U.S.C. 103(a) as being unpatentable over Michetti (WO95/22987) in view of Russell et al (US Pat. 6,030,624) is argued:

"However, the cited references contain no suggestion or motivation for providing the immunological protection of the present invention."

"no teaching or suggestion is provided for a protective oral live vaccine consisting of an attenuated bacterial carrier that expresses a Helicobacter immunogen on its own (non-chimeric)"; and

the instant invention is able to "induce protective immunity of about 100% after a single dose application without use of additional adjuvants" and Russell uses cholera toxin A2/B as an adjuvant.

26. Applicant's arguments filed with respect to Michetti in view of Russell have been fully considered but they are not persuasive because applicant's arguments are not commensurate in scope with the claimed invention. The instant invention recites open language which permits the presence of other components in the compositions, such as adjuvants, and the methods would provide for the use of additional reagents and methods steps for the attainment of the desired immune response.

The phrase "*immunological protection of the present invention*", is being read to mean immunological protection against Helicobacter infection. Clearly Michetti in view of Russell teach, provide guidance and motivation for the construction of recombinant attenuated microbial pathogens, that comprise a recombinant AroA attenuated mutant Salmonella transformed to express a heterologous Helicobacter immunogen for the induction of a protective immune response directed against Helicobacter, a pathogen known to be associated with gastric ulcers. If an asserted meaning other than that read by the examiner for the quoted phrase above, the examiner would appreciate clarification of this argument relative to the claimed invention.

The claimed invention does not exclude the use of chimeric heterologous immunogens and therefore permits that inclusion of compositions that would encode more than one heterologous antigen.

Arguments directed to the wherein statement recited in claim 21, " wherein the composition is administered as a single dose" does not exclude the administration of additional doses. Claim 21 defines the composition of claims 19 and 20 is administered as a single dose, but the method may comprise the administration of multiple doses because the claims recite "comprising language" and the methods could comprise additional administration steps.

The rejection over Michetti in view of Russell is maintained for reasons of record.

27. The rejection of claims 1-4,7-11 under 35 U.S.C. 103(a) as being unpatentable over Russell et al (US Pat. 6,030,624) in view of Bukanov et al (1994) is argued

to " provide no suggestion or motivation regarding the Helicobacter immunogen or live vaccine of the present invention."

"Russell et al. does not teach or suggest an attenuated pathogen comprising a Helicobacter immunogen that is capable of inducing protective immunity ";

the instant invention is " capable of inducing protective immunity of about 100% after a single dose application" and

"Bukanov et al fails to cure any of the deficiencies of Russell et al."

28. Applicant's arguments filed with respect to Russell in view of Bukanov have been fully considered but they are not persuasive.

The phrase "*immunological protection of the present invention*", is being read to mean immunological protection against Helicobacter infection. Clearly Russell suggests, teaches, and provides guidance for the construction of a recombinant attenuated microbial pathogens, that comprise a recombinant AroA attenuated mutant Salmonella transformed to express a heterologous Helicobacter immunogen for the induction of a protective immune response directed against Helicobacter, a pathogen known to be associated with gastric ulcers (col. 9, lines 46 and 66).

Russell et al suggest the formulation of vaccine compositions for Helicobacter. Vaccine antigens induce protective immunity. Bukanov was cited for what the reference taught with respect to known Helicobacter antigens and their use in the production of recombinant attenuated microbial pathogens. Bukanov taught the person of ordinary skill that urease nucleic acid sequences were known and could be incorporated into a attenuated microbial pathogen for expression. At the time of filing of the instant Application, urease was known to be a protective Helicobacter antigen. The person of ordinary skill in the art at the time the invention was made would have been motivated to use a known protective Helicobacter immunogen in the formulation of a recombinant attenuated microbial pathogen for the induction of a protective immune response.

Arguments directed to the wherein statement recited in claim 21, " wherein the composition is administered as a single dose" does not exclude the administration of additional doses. Claim 21 defines the dose of claims 19 and 20 as a single dose, but the method may comprise the administration of multiple doses because the claims recite "comprising language" and the methods are not limited to only a single administration step. Applicant's arguments are not commensurate in scope with the claimed invention.

The rejection of Russell in view of Bukanov is maintained for reasons of record.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

29. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

30. Claims 1-11, 13-15, 17-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is directed to any composition of an attenuated Salmonella cell that encodes a heterologous Helicobacter immunogen, and claims 11, 17 and 18 depend therefrom, which define the composition to be a living vaccine. Claim 1 therefore may be living or dead since claims 17

and 18 define the cell to be living and seek to further limit the composition of claim 1 . If the cell of claim 1 is attenuated through cell death, how will it be capable of expressing the encoded Helicobacter immunogen? Clarification of the cell as being a living or dead cell relative to the recited functional limitations defining capabilities is requested.

Claim 1 recites the phrase "said nucleic acid molecule in a transformed target cell". Is the nucleic acid molecule only expressed in target cells that have been previously transformed, or does the nucleic acid molecule transform the target cell? What defines a target cell? How or with what has the target cell been transformed? What is the relationship of the recombinant attenuated Salmonella cell and the transformed target cell; are they one in the same cell? How do the recombinant cell and the transformed cell differ one from the other?

Claim 2 broadens the scope of claim 1 and is therefore not further limiting. The claim recites the phrase "especially a Salmonella cell". This phrase does not distinctly claim Applicant's invention in view of claim 1 reciting the term "Salmonella". What other enterobacterial cells are intended?

Claims 2-4, 8-11, 13-15, 17-21 recite the phrase "the pathogen", "the attenuated pathogen" or "said pathogen", and depend from claim 1. These phrases lack antecedent basis in claim 1 which does not define the attenuated cell as being pathogenic. The phrase "attenuated pathogen" broadens the scope of claim 1 as the claims are not limited to Salmonella, but must only use an attenuated pathogen which could include not only attenuated Salmonella, but also attenuated enterobacterial or viral pathogens.

Claim 6 recites the phase "Helicobacter antigen" and depends from claim 1. This phrase lacks antecedent basis in claim 1 which recites "Helicobacter immunogen". How can an immunologically reactive fragment define a protective immunogen if it is not immunogenic, and is only immunoreactive? An immunologically reactive fragment broadens the scope of claim 1 to include epitopes that are not immunogens. Claim 6 recites species that are not further limiting of the base claim.

Claim 6 recites the phrase "selected from the group consisting of" and then recites species A, B, C or D. Markush group format is defined by the recited phrase and the species being A, B, C and D.

Claim 7 recites the phrase "capable to be expressed". What structural components present in the cell define this capability? No promoters or nucleic acid molecules that regulate expression are present to define the recited capability; the invention is not distinctly claimed. What components of the cell define the capability "to be expressed phase variably"? What phases do the cell express variably? How and when is the Helicobacter immunogen expressed? How is the effective amount administered if phase variable expression is not induced? Clarification of the invention is requested.

Claim 8 defines a "nucleic acid reorganization" mechanism. What is this mechanism? Is the reorganization essential for the effective amount of immunogen to be expressed? Which of the nucleic acids is activated, serves as the expression signal, and encodes a Helicobacter immunogen in light of the "capability" referring back to various nucleic acid molecules from

multiple sources. Clarification, of what activates, remains inactive and how expression is accomplished in order to administer an effective amount of immunogen, is requested.

Claim 9 defines the activation event to be "caused by a DNA reorganization". What DNA is reorganized, how is it reorganized and what is the expression signal that promotes the activation for reorganization ? Is this reorganization essential for expression of Helicobacter immunogen? If the reorganization is essential, how can the amount of cell administered be an effective amount if the amount is contingent upon some future reorganization event that has not taken place and may not be activated? Clarification of the various components of the claimed composition is requested.

Claim 10 recites the phrase "capable to express". This phrase is in the further tense, what is missing or what is present to define the pathogen "to express" the polypeptide? Clarification of what defines the pathogen as being "capable to express" the polypeptide is requested.

Claims 19-21 administer an effective amount to induce protective immunity. The type of protective immunity induced is not distinctly claimed. What is the protective immunity against in light of the cell being a Salmonella cell ?

Claim 21 defines the dose to be a single dose and depends from claims 19 or 20 which only recite a single methods step. How does claim 21 further limit claims 19 and 20 that only administer a single dose?

Claims 13, 20-21 and 22 recite the phrase an "effective amount" of the cell. What is the amount effective for? The cell defines the "effective amount". The cell is a salmonella cell. Is

the protective immunity induced directed against the effective salmonella cell? The protective immunity induced is not distinctly claimed.

Claim Rejections - 35 USC § 102

31. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

Please Note: the phrase "secretory polypeptide" is being read to include polypeptides that are secreted by Helicobacter into the external environment, which would include Helicobacter urease.

32. Claims 1, 2, 4-5, 7-8, 10-11, 17-18 are rejected under 35 U.S.C. 102(e) as being anticipated by Michetti et al (US Pat. 6,290,962, filing date Feb. 1994).

(composition claims) The claimed invention is directed to a recombinant attenuated Salmonella composition that comprises a heterologous Helicobacter nucleic acid molecule encoding a Helicobacter urease immunogen (instant claims 1, 2, 4-5), or the enterobacterial cell that includes an expression system directed to a targeted cell (claims 1,2,7-8) , wherein the composition is

formulated together with a second nucleic acid molecule that is a immunomodulatory polypeptide (claim 10), or formulated together with a diluent, carrier or adjuvant (claim 11, 17 and 18).

Michetti et al (US Pat. 6,290,962) disclose a recombinant attenuated (see col. 9, lines 24-25) Salmonella (see claims 52 and 67, as well as col. 9, lines 23-24) composition that comprises a heterologous Helicobacter nucleic acid molecule encoding a Helicobacter urease immunogen (See Michetti claims 41-70), as well as an attenuated cell that includes an expression system for directed expression of the encoded Helicobacter nucleic acid in a targeted cell (See Michetti, claims 51-53, 66-68) , wherein the composition is formulated together with a second nucleic acid molecule that is an immunomodulatory polypeptide (see Michetti, claims 45-46,51, 60-61), or formulated together with a diluent, carrier or adjuvant (see Michetti claims 46-50, 60-66).

Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594

Inherently the reference anticipates the now claimed invention. Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states "Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's

functioning, does not render the old composition patentably new to the discoverer. "The Court further held that "this same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art".

33. Claims 1, 13-15, 19-22 are rejected under 35 U.S.C. 102(e) as being anticipated by Michetti et al (US Pat. 6,290,962, filing date Feb. 1994).

(method claims) The claimed invention is directed to methods of preparing (claims 13-15) and methods of using (claims 19-22) a recombinant attenuated Salmonella, enterobacterial cell or attenuated pathogen composition that comprises a heterologous Helicobacter nucleic acid molecule encoding an immunogen (claim 1).

The methods of preparing a composition comprise the steps of :

providing the attenuated Salmonella, enterobacterial cell or attenuated pathogen composition that encodes a Helicobacter immunogen; and

formulating the attenuated pathogen into a composition with a diluent, carrier or adjuvant.

The methods of using the composition for inducing a protective immune response to treat or prevent infection, the method comprises the step of:

administering the composition that comprises an attenuated Salmonella, enterobacterial cell or attenuated pathogen composition that encodes a Helicobacter immunogen.

Michetti et al (US Pat. 6,290,962) disclose methods of preparing compositions that comprise the steps of :

providing an attenuated Salmonella, enterobacterial cell or attenuated pathogen composition that encodes a Helicobacter immunogen (see col. 9, lines 23-25 and see claims 52 and 67); and

formulating the attenuated pathogen into a composition with a diluent, carrier or adjuvant (see col. 8, lines 63-65 and col. 9, lines 35-65).

Michetti et al (US Pat. 6,290,962) disclose methods of using an attenuated pathogen for inducing a protective immune response, that results in treating or preventing infection the methods comprise the step of:

administering the composition that comprises an attenuated Salmonella, enterobacterial cell or attenuated pathogen composition that encodes a Helicobacter immunogen. (see col. 12, lines 16-32; col. 13, lines 56-67 and col. 14, lines 1-14; col. 18, lines 28-49; claims 1-40 and claims 71-72).

Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594

Inherently the reference anticipates the now claimed invention. Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states "Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. "The Court further held that "this same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art".

34. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242. The Group and/or Art Unit location of your application in the PTO will be Group

Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp
March 11, 2002

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